JACC Vol. 13, No. 3
March 1, 1989:567–73

Relation Between Exertional Ischemia and Prognosis in Mildly Symptomatic Patients With Single or Double Vessel Coronary Artery Disease and Left Ventricular Dysfunction at Rest

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The randomized multicenter trials indicate that survival in patients with coronary artery disease and left ventricular dysfunction is enhanced by surgical therapy compared with medical therapy. This beneficial effect of coronary bypass surgery was demonstrated in patients with either three vessel or left main coronary artery disease, but not in those with one or two vessel disease. To determine whether subgroups of mildly symptomatic patients with one or two vessel coronary artery disease and left ventricular dysfunction have an increased risk of death or cardiac events during medical therapy, 53 consecutive patients with angiographically defined one or two vessel disease and impaired left ventricular function (ejection fraction 20% to 40%) were studied by exercise electrocardiography (ECG) and rest and exercise radionuclide angiography. All but two patients had previous myocardial infarction, and all were asymptomatic or only mildly symptomatic during medical therapy.

By univariate life table analysis, mortality during medical therapy was associated significantly with the ST segment response to exercise ($p < 0.05$) and with both the exercise ejection fraction ($p < 0.05$) and the magnitude of change in ejection fraction with exercise ($p < 0.005$). In patients with an exercise ejection fraction >30%, the probability of survival at 6 years was 97 ± 3% (±SE) compared with a survival rate of 62 ± 14% in the remaining subjects ($p < 0.005$). Similarly, 6 year survival was 100% in patients whose ejection fraction increased from the value at rest but was only 74 ± 10% in the remaining patients ($p < 0.005$). Exercise capacity was not associated with survival. The likelihood of a cardiac event (death, reinfarction or congestive heart failure) during medical treatment was also associated significantly with the exercise ejection fraction and magnitude of change in ejection fraction with exercise (both $p < 0.005$). Twelve of the 18 events, including seven of the eight deaths, occurred in patients with two vessel disease.

Therefore, noninvasive indexes of left ventricular function and myocardial ischemia are important predictors of the clinical course of mildly symptomatic patients with two vessel disease and left ventricular dysfunction at rest, and may be used to identify subgroups of patients at risk of death, as well as of major cardiac events, during subsequent medical therapy.

(J Am Coll Cardiol 1989;13:567–73)

There is convincing evidence that, in selected groups of mildly symptomatic patients with coronary artery disease, coronary artery bypass surgery increases life expectancy. Recent multicenter trials of medical versus surgical treatment of coronary artery disease (1–11), as well as related investigations (12–14), have identified subgroups of patients whose prognosis is enhanced by surgical treatment in comparison with medical therapy. Mildly symptomatic patients with significant stenosis of the left main coronary artery (1,2), as well as those with three vessel disease and left ventricular dysfunction at rest (6,7,11,13), have improved long-term survival if treated surgically.

In the Coronary Artery Surgery Study (CASS), the improved long-term survival in patients with three vessel disease and impaired left ventricular function was observed primarily in patients with exercise-induced angina, exercise-induced ST segment depression or reduced exercise tolerance (8,15,16). This observation suggests that inducible

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Manuscript received May 31, 1988; revised manuscript received September 22, 1988, accepted October 14, 1988.

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0735-1097/89/$3.50

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ischemia, superimposed on previous left ventricular damage, is of major importance in determining the prognosis of patients who have similar degrees of ventricular dysfunction at rest. If this is the case, then higher mortality rates during medical therapy might also be expected in patients with one or two vessel disease and left ventricular dysfunction who manifest inducible ischemia compared with rates in similar patients with one or two vessel disease but without inducible ischemia. The present investigation was undertaken to determine whether in mildly symptomatic patients with coronary artery disease and left ventricular dysfunction at rest, noninvasive indexes of left ventricular function and exercise-induced ischemia are related to prognosis in the subgroup of patients with one or two vessel disease.

Methods

Study patients. Between June 1976 and January 1986, we studied prospectively 53 consecutive asymptomatic or mildly symptomatic patients with angiographically defined one vessel or two vessel coronary artery disease and left ventricular dysfunction at rest, with rest ejection fraction by radionuclide angiography between 20% and 40%. Patients were included in this study if they were <70 years of age and had not undergone previous coronary artery bypass surgery. Coronary angiograms were obtained with the percutaneous femoral technique in multiple left anterior oblique and right anterior oblique projections. Significant coronary artery stenosis was defined as a ≥50% reduction in luminal diameter (in comparison with the diameter of the artery just proximal to the stenosis) of at least one epicardial coronary artery. Twenty-two patients (42%) had stenosis of one coronary artery and 31 (58%) of two major coronary arteries. There were 41 men and 12 women ranging in age from 25 to 69 years (mean 51). Twenty-five patients had only mild angina pectoris (Canadian Heart Association class II), and the other 28 patients were completely asymptomatic during medical therapy.

Fifty-one patients (96%) had evidence of a previous myocardial infarction, as documented by at least two of the three following criteria: 1) abnormal Q waves in the basal electrocardiogram (ECG) or clear ECG documentation of the acute phase of the infarction; 2) documentation of serial elevations of serum creatine kinase or kinase MB isoenzyme; and 3) history of typical, prolonged chest pain. The site of the infarction was anterior (leads I, aVL, V_1 to V_6) in 22 patients and inferior (leads II, III, aVF) in 19; in the other 9 patients, the site of infarction could not be localized by ECG, or there was evidence of multiple infarctions or of non-Q wave infarction.

All patients underwent exercise ECG and rest and exercise radionuclide angiography. Coronary arteriography was performed within 1 month of radionuclide angiography and exercise testing in all but eight patients; within 6 months of exercise studies in four of these latter eight patients and within 12 months in the other four patients. Three of these four patients subsequently underwent repeat coronary arteriography with confirmation of the previous results; the patient who did not undergo repeat coronary arteriography had two vessel disease. In this particular patient, angina did not change in intensity or frequency during the interval between noninvasive studies and coronary arteriography.

Exercise testing. All exercise studies were performed after withdrawal of all cardiac medications and, in particular, ≥48 h after discontinuation of propranolol and calcium channel blocking drugs and ≥12 h after discontinuation of nitrate preparations.

Gated blood pool cardiac scintigraphy. Rest and symptom-limited exercise radionuclide angiograms were obtained in the supine position. Exercise studies were performed with a bicycle ergometer beginning at a work load of 25 W. Work loads were increased by 25 W increments every 2 min; heart rate and blood pressure measured by sphygmomanometry were monitored during exercise. Imaging was begun early after the start of exercise, but only that portion of the data obtained during maximal exercise was selected for analysis. Left ventricular ejection fraction was determined by computer analysis of the scintigraphic data, as previously described (17).

Exercise electrocardiography. The patients performed symptom-limited exercise after withdrawal of medications during the same week as radionuclide angiography. We used an upright bicycle ergometer in 46 patients; work loads were increased by 20 W increments every 3 min. To determine the initial work load for this test, two training sessions were carried out for every patient, and the initial work load for the final test was chosen such that an end point could be reached after 3 to 5 min of exercise (18,19). The remaining seven patients underwent treadmill exercise testing. In the absence of any symptoms, tests were interrupted when heart rate reached 85% of the predicted maximal value for age and gender. Two bipolar ECG leads were monitored during exercise, as previously described (20); ECGs were obtained at rest, during exercise and for 5 min after termination of exercise. ST segment depression was measured 0.08 s after the J point; only flat or downsloping depressions of ST segment ≥0.1 mV were considered ischemic changes. In patients with ST segment abnormalities at rest, a further decrease in ST segment of ≥0.1 mV was also considered an abnormal response. ST segment interpretation was not possible in five patients because of excessive baseline artifacts (four patients) or bundle branch block (one patient).

Ambulatory electrocardiographic monitoring. In a subset of 34 patients, 24 h ECG recordings were obtained, as previously described (21). This procedure was performed after withdrawal of all medications.

Follow-up evaluation. During the course of this study, coronary artery bypass surgery or percutaneous coronary

Table 1. Association Between Noninvasive Exercise Data and Subsequent Clinical Course in 53 Patients

	Deaths (8 events): p Value	Death or Reinfarction (10 events): p Value	Death, CHF or Reinfarction (15 events): p Value	Any Cardiac Event (18 events): p Value
Age (yr)	0.72	0.87	0.69	0.82
Gender	0.79	0.84	0.52	0.37
Exercise ECG testing				
ST segment response	0.03*	0.02*	0.12	0.02*
Exercise capacity	0.19	0.09	0.02	0.02*
Angina during exercise	0.14	0.32	0.65	0.39
Radionuclide angiography				
LVEF at rest	0.41	0.48	0.08	0.23
LVEF during exercise	0.02*	0.04*	0.003*	0.007*
LVEF response to exercise†	0.003*	0.006*	0.003*	0.002*
Ambulatory ECG monitoring				
Lown class	0.42	0.77	0.96	0.56
Presence of ventricular tachycardia	0.76	0.72	0.94	0.45
Length of ventricular tachycardia	0.51	0.96	0.88	0.37

*Significant value by Cox univariate analysis (22); †ejection fraction during exercise minus ejection fraction at rest. CHF = congestive heart failure; ECG = electrocardiographic; LVEF = left ventricular ejection fraction.

angioplasty was performed only when angina increased in severity and became symptomatically limiting despite therapy with beta-adrenergic blocking drugs, nitrate preparations and, since 1980, calcium channel blocking drugs. Patients who became candidates for operation on the basis of increasing symptoms were admitted for repeat coronary arteriography.

Statistical analysis. The ability of noninvasive data to predict the subsequent clinical course during medical therapy was assessed by Cox regression analysis (22). The noninvasive variables considered in this analysis included gender, age, rest and exercise ejection fraction, magnitude of change in ejection fraction during exercise (exercise value minus rest value), exercise capacity (expressed in watts), ST segment response to exercise, reasons for terminating exercise, and the presence or absence of ventricular tachycardia and Lown class of ventricular arrhythmias (23) on ambulatory ECG monitoring. Cardiac events in this analysis included: 1) death during medical treatment, 2) death, reinfarction or congestive heart failure, and 3) death, reinfarction, congestive heart failure or increasing angina requiring surgery. Congestive heart failure was defined as the development of dyspnea under rest conditions (New York Heart Association functional class IV). Patients who underwent coronary bypass surgery were censored from the survival and survival plus reinfarction or heart failure analyses at the date of surgery. We plotted survival curves using the method of Kaplan and Meier (24); the differences among subgroups were analyzed with use of the Mantel-Haenszel test (25). We used discriminant analysis (26) to determine the best cutoff limits for exercise left ventricular ejection fraction and exercise capacity with which to subgroup patients for this analysis.

Results

Patient experience. During the course of medical therapy with a mean follow-up of 56 ± 30 months, eight patients died: four patients died suddenly (three with two vessel and one with one vessel disease); two patients (both with two vessel disease) died from refractory heart failure after reinfarction; and two patients (both with two vessel disease) died from unknown causes in the absence of witnesses. One of these latter deaths was thought to be of cardiac origin because the patient developed progressive symptoms of heart failure and angina during medical treatment and had no other known life-threatening illnesses. The remaining patient disappeared while sailing.

Three patients had a nonfatal myocardial reinfarction and seven developed overt heart failure. Including the eight deaths, 15 patients had at least one of these major cardiac events. Four of these patients and an additional three other patients underwent bypass surgery for increasing symptoms.

Determinants of prognosis. The association by univariate Cox regression analysis between the noninvasive exercise data and these end points is shown in Table 1. Only the ST segment response ($p < 0.05$) and the radionuclide angiographic variables, including the ejection fraction during exercise ($p < 0.05$) and the magnitude of change in ejection fraction with exercise compared with the rest value ($p < 0.005$), were associated significantly with death during medical therapy. In addition, both of the exercise radionuclide

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Table 2. Clinical Course in 53 Patients With One Vessel or Two Vessel Disease

	Number of Patients	Percent Alive at 6 Years	p Value	Percent Alive at 6 Years Without CHF or Reinfarction	p Value	Percent Alive at 6 Years Without Cardiac Events	p Value
All patients	53	86 ± 5		83 ± 6		69 ± 7	
Exercise EF							
>30%	36	97 ± 3		89 ± 5		81 ± 7	
			<0.005*		<0.005*		<0.005*
≤30%	17	62 ± 14		47 ± 13		44 ± 12	
Change in EF with exercise							
Increase	22	100		95 ± 4		89 ± 7	
			<0.005*		<0.005*		<0.005*
No change or decrease	31	74 ± 10		60 ± 9		53 ± 10	
ST segment response to exercise							
Normal (<0.1 mV)	33	90 ± 5		77 ± 8		77 ± 8	
			0.15		0.36		0.057
Abnormal (≥0.1 mV)	15	75 ± 13		71 ± 2		50 ± 14	
Exercise capacity							
≥100 W	26	91 ± 7		77 ± 9		80 ± 8	
			0.33		0.11		0.059
<100 W	20	84 ± 8		69 ± 11		55 ± 12	

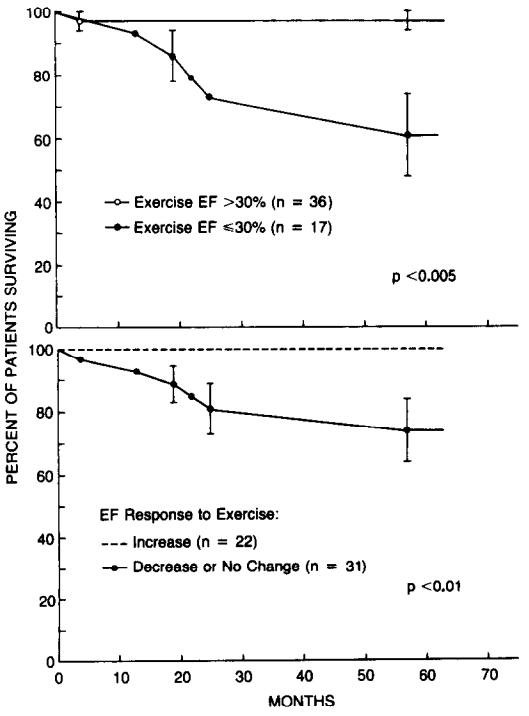
*Significant values by Mantel-Haenszel test (24). EF = ejection fraction; other abbreviations as in Table 1. Values shown are mean values ± SE.

angiographic variables as well as the ST segment response and exercise capacity were associated with death, heart failure, reinfarction or increased angina requiring surgical intervention.

When the patients were classified into discrete subgroups to evaluate survival and cardiac event trends during the follow-up period (Table 2), both the exercise ejection fraction and the magnitude of change in ejection fraction during exercise compared with the value at rest were associated significantly with survival. In patients with an ejection fraction during exercise >30%, the survival at 6 years was 97% ± 3% compared with 62% ± 14% in patients with an exercise ejection fraction of ≤30% ($p < 0.005$) (Fig. 1), representing annual mortality rates of 0.5% and 6.3%, respectively. Similarly, the 6 year survival rate of patients whose ejection fraction increased with exercise compared with the value at rest was excellent (100%) and significantly greater than that of patients whose ejection fraction was unchanged or decreased during exercise (Table 1, Fig. 1); the respective annual mortality rates in these subgroups were 0% and 4.3%. When patients were classified on the basis of left ventricular ejection fraction at rest, presence or absence of ST segment depression with exercise, or exercise capacity, no significant differences in survival were observed among subgroups.

The radionuclide angiographic data during exercise remained significantly related to the outcome when myocardial infarction and congestive heart failure in addition to death were considered (Table 2), as was the case when

Figure 1. Influence of left ventricular ejection fraction (EF) during exercise and the ejection fraction response to exercise on subsequent survival during medical treatment. **Top,** Survival of patients with an ejection fraction during exercise >30% is compared with that of patients with ejection fraction ≤30%. **Bottom,** Survival in patients with an increase in ejection fraction relative to the value at rest is compared with that of patients in whom ejection fraction was unchanged or decreased during exercise. Bars indicate ±SE.



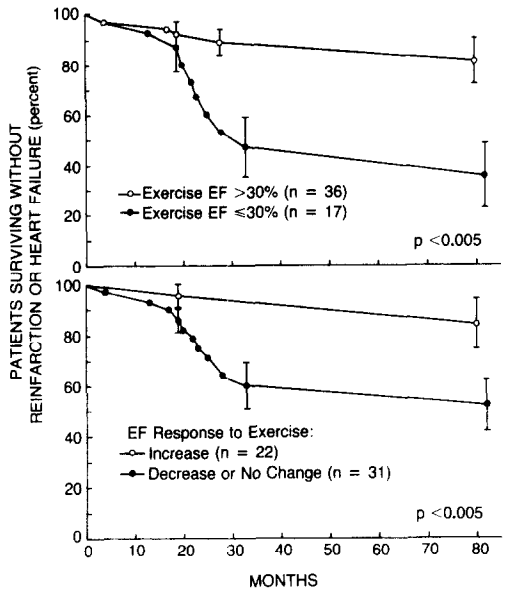


Figure 2. Influence of left ventricular ejection fraction (EF) response during exercise and the likelihood of death, reinfarction or heart failure. Patients are classified as in Figure 1.

increased angina requiring surgery was also included in the analysis. In patients with greater functional abnormalities during exercise, the risk of death, reinfarction or heart failure within 6 years was very high (Table 2, Fig. 2); within 6 years, 53% of patients with an exercise ejection fraction ≤30% experienced such cardiac end points, as did 40% of patients whose ejection fraction failed to increase during exercise compared with the rest value.

Patients with two vessel disease. Twelve of the 18 cardiac events, including seven of the eight deaths, occurred in the 31 patients with two vessel disease. Because of the small number of events, no variable was predictive of outcome in patients with one vessel disease. An analysis of the patients with two vessel disease, however, indicated that survival was significantly associated with the magnitude of change in ejection fraction during exercise compared with the rest value ($p = 0.03$). The ST segment response ($p = 0.15$) and the ejection fraction during exercise ($p = 0.06$) were not associated significantly with survival.

When patients with two vessel disease were classified into discrete subgroups, survival trends were similar to those observed in the total cohort of patients with either one vessel or two vessel disease. Patients with two vessel disease and exercise ejection fraction >30% had higher 6 year survival rates than did those with exercise ejection fraction of ≤30% (95% ± 5% versus 58% ± 16%, $p < 0.05$). Similarly, patients manifesting an increase in ejection fraction during exercise compared with rest values had higher 6 year survival rate than did those whose ejection fraction was unchanged or decreased (100% versus 67% ± 13%, $p < 0.05$).

Effect of left anterior descending coronary artery stenosis. Thirty-nine (74%) of the 53 patients had stenosis of the left anterior descending artery, including 14 (64%) of the 22 patients with one vessel disease and 25 (81%) of the 31 patients with two vessel disease. All deaths occurred in patients with stenosis of the left anterior descending artery. Because of the small number of patients without involvement of this artery (14 patients), a comparison of patients with versus those without such stenosis was not performed.

Discussion

Among patients with coronary artery disease, survival is reduced in patients with left ventricular dysfunction at rest compared with that in patients with preserved left ventricular function (3,27,28). Recently, investigators in the CASS (7,11) and Veterans Administration (6) trials and in the Seattle Heart Watch (13) have demonstrated that, in mildly symptomatic patients with three vessel disease and left ventricular dysfunction at rest, survival may be enhanced by coronary bypass surgery. Survival is also improved by surgery in patients with left main coronary artery disease and depressed left ventricular function (1,2). However, enhanced survival by surgical therapy has not been demonstrated in mildly symptomatic patients with one or two vessel disease and impaired left ventricular function (6,13). The purpose of the current investigation was to determine whether there are subgroups of mildly symptomatic patients with left ventricular dysfunction and either one or two vessel disease who have an increased risk of death, reinfarction or heart failure during medical therapy.

Exercise-induced ischemia and prognosis. Our data indicate that the left ventricular functional response during exercise is predictive of prognosis in patients with one or two vessel disease and left ventricular dysfunction. Those patients with no change or a decrease in ejection fraction during exercise are at high risk of dying (Fig. 1) or of experiencing a major cardiac event (Fig. 2), whereas those whose ejection fraction increases during exercise compared with the value at rest are at low risk during medical therapy, despite impaired left ventricular function. In this regard, ejection fraction was lower during exercise than at rest in all patients in our series who died during the follow-up period, and was <30% during exercise in all but one patient. Although the ST segment response in our study was also associated with outcome (Table 1), other variables derived from exercise testing, such as exercise capacity or the development of angina pectoris, were not helpful in selecting subgroups at greater risk of dying during the follow-up period. The degree of left ventricular dysfunction at rest and ventricular arrhythmias on ambulatory monitoring were also not associated with subsequent outcome.

In more symptomatic patients with wider ranges of left ventricular function at rest, Pryor et al. (29) also observed

that exercise ejection fraction was the variable most closely associated with future cardiac events; and Higginbotham et al. (30) demonstrated in unselected patients with coronary artery disease and an ejection fraction of <50% that a decrease in ejection fraction with exercise was significantly associated with late mortality during medical treatment. In neither of these two studies were the data in patients with one vessel or two vessel disease analyzed separately, and patients with moderate to severe symptomatic limitation were included in both studies. Data derived from the CASS randomized trial (7) in patients with left ventricular dysfunction did not identify high risk and low risk subgroups with one or two vessel disease. However, the number of such patients undergoing randomization in that multicenter trial was quite small: only 11 patients with one vessel disease and 35 patients with two vessel disease were randomized to medical treatment in the CASS study (fewer patients than in our study). In that investigation, moreover, exercise studies were not performed in all patients. Of the patients who did exercise, medications were not routinely discontinued and the left ventricular functional response to exercise was not assessed.

Recent data from the CASS registry (15,16) indicate that the patients with three vessel disease and impaired left ventricular function who manifest the poorest survival (and also greatest benefit from surgery) are those patients with ST segment abnormalities induced at low work loads of treadmill exercise. These data suggest that inducible myocardial ischemia superimposed on previous left ventricular damage is of major importance in determining prognosis in such patients. Our data indicate that similar factors influence prognosis in patients with left ventricular dysfunction and two vessel disease.

Limitations of the study. Several limitations of our study should be addressed. Because seven of the eight deaths occurred in patients with two vessel disease, our data are inconclusive in those with one vessel disease. All deaths in our series occurred in patients with stenosis of the left anterior descending artery, but the small number of patients without such involvement did not allow us to test the possibility that left anterior descending disease adversely affects prognosis in patients with left ventricular dysfunction at rest. Medical therapy was not standardized in a rigorous fashion in that patients received a variety of beta-adrenergic blocking drugs, calcium channel blockers and nitrate preparations in different doses. Aspirin and lipid-lowering drugs were not used consistently. Such limitations in medical therapy are present in the multicenter randomized trials as well. Because our data were derived from a relatively small patient sample with a limited number of deaths our conclusions must be considered tentative until confirmed by a larger series. Finally, we do not have data on a corresponding series of patients undergoing coronary bypass surgery to demonstrate whether surgery improves survival in our high risk groups.

Conclusions. Despite these limitations, our results indicate that the left ventricular functional response to exercise provides critically important data for determining the risk stratification of mildly symptomatic patients with two vessel disease and left ventricular dysfunction at rest and may prove of value in identifying such patients, as well as those with three vessel disease, who warrant more aggressive management.

We thank Imogene Surrey and Maude Atcheson for excellent editorial assistance.

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